## REMARKS/ARGUMENTS

With entry of this amendment, claims 1, 6-12, and 29-39 are pending in the above-identified application. Claims 2-5 and 13-28 are canceled without prejudice to Applicants' right to prosecute the subject matter of these claims in a related, co-pending application. Claims 1, 6-8, 10, and 12 are amended and new claims 29-39 are added as set forth in detail below. Support for these amendments is identified in the following remarks. No new matter is added. Examination and reconsideration of all pending claims are respectfully requested.

### Information Disclosure Statement

Applicants will shortly submit an Information Disclosure Statement under 37 CFR §1.97 and §1.98, forms PTO/SB/08A and PTO/SB/08B listing the cited references and copies of the cited foreign patent documents and non-patent documents for the Examiner's consideration.

### Double Patenting

Claims 1-5 and 8-12 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over each of the following:

(1) claims 1, 2, 5, and 8-10 of U.S. Patent No. 6,376,475 in view of Tsuji (*J. Biochem.* 1:1-14, 1996);

(2) claims 1-3, 6-9, and 41-43 of co-pending Application No. 10/131,721; and

(3) claims 1-11, 16-20, and 25 of co-pending Application No. 10/398,520.

Applicants believe these rejections to be obviated by the present amendments to claim 1. Independent claim 1 now recites, *inter alia*, "administering to the animal an effective dose of an inhibitor of ST3Gal-IV sialyltransferase enzyme activity, wherein said animal is suffering from or is at risk of developing atherosclerosis or a blood clotting disorder." The Examiner has not shown how any of the claims cited above would motive one of skill in the art

atherosclerosis or a blood clotting disorder, as presently recited in claim 1. Accordingly, Applicants believe the present claims to be patentably distinct from the cited claims of U.S. 6,376, 475, Application No. 10/131,721, and Application No. 10/398,520. Withdrawal of these rejections is respectfully requested.

**Rejections under 35 U.S.C. § 112, first paragraph**

Claims 1-12 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description and enablement requirements. These rejections are based primarily on the Examiner's contention that the specification does not adequately disclose "agents" that will function in the method as claimed. Both rejections are overcome in part and traversed in part as set forth below.

As an initial matter, while not agreeing with the Examiner's rejections nor reasons for rejection, but in order to further expedite prosecution of the instant application, independent claim 1 is amended to specify "an inhibitor of ST3Gal-IV sialyltransferase enzyme activity." Support for this amendment is found in the specification, *e.g.*, at page 13, lines 7-25, and in original claim 5. In view of this amendment, dependent claims 2-5 are canceled without prejudice and dependent claims 6-8, 10, and 12 are amended accordingly

In view of the present amendments to claim 1, the rejections of the claims for alleged lack of written description and enablement are obviated as they pertain to antisense nucleic acids. Therefore, Applicants will address the Examiner's remarks only as they relate to enzymatic inhibitors of ST3Gal-IV sialyltransferase.

Further, before addressing the Examiner's specific remarks, Applicants note that the present invention is ***not*** the discovery of ST3Gal-IV sialyltransferase inhibitors. Rather, the invention, as presently claimed, is based on the discovery that agents that have this function can be used in methods to modulate levels of vWF or FVIII in an animal. This association between ST3Gal-IV sialyltransferase activity and levels of vWF or FVIII, which is set forth in detail in the specification as filed, had not been previously described.

In particular, Applicants' inventive insight was achieved, *inter alia*, through studies using transgenic mice deficient in ST3Gal-IV sialyltransferase. Desialyation of vWF had previously been shown to result in more rapid clearance of vWF, and it had been hypothesized that this effect was due to the exposure of terminal galactose residues. However, the specific sialyltransferase enzymes responsible for sialylation of vWF *in vivo* had not been previously identified. (*See* specification at page 3, lines 17-26.) As described in the Results and Discussion sections of Example 1 (*see* pages 33-39), ST3Gal-IV deficient mice showed a loss of a subset of terminal $\alpha$2,3 sialic acids from cell surface glycoproteins, exposing terminal galactose residues. These mice also showed an autosomal dominant effect of the loss of ST3Gal-IV on vWF and its associated molecule, FVIII, without affecting platelet formation. (*See id.*) Because vWF and FVIII are risk factors for arterial disease and related disorders, this effect of ST3Gal-IV deficiency indicated ST3Gal-IV as a good target for drug therapy.

Applicants therefore recognized that inhibition of ST3Gal-IV sialyltransferase would have therapeutic and prophylactic benefits for, *e.g.*, atherosclerosis and blood clotting disorders. Since glycosyltransferases are well-studied and many inhibitors of these enzymes are known, Applicants also recognized that any of a number of means of inhibiting the activity of sialyltransferases could be used in the invention. As described in the specification, enzymatic inhibitors of sialyltransferases were well-known in the art (*see* specification at page 13, lines 7-25 (citing references)), and routine methods of screening for inhibitors are also disclosed in the specification (*see* page 14, line 5, to page 15, line 10).

***Written Description***

As indicated above, the rejection of the claims for alleged lack of written description is based generally on the Examiner's assertion that the specification fails to describe "the agent ... of the invention as claimed." In this regard, the Examiner sets forth various contentions, as to the guidance provided in the specification, as allegedly supporting this rejection. In particular, the Examiner asserts, *inter alia*, the following:

(1) that the method relies on a function for agent "for which a structure that corresponds with said function is not adequately described";

(2) that the specification provides "no specific guidance that would lead one skilled in the art to a specific molecule" that would function in the claimed method; and that the skilled artisan "cannot envision an exact structure" for any inhibitory ... agent" to be used in the claimed method; and

(3) that when claims are drawn to a genus, written description requires more than disclosure of a single or several species of the invention, and that in this case "no species of the invention are disclosed as agents ... that function in the method of treatment as claimed."

First, the underlying inquiry with regard to written description is ***not*** whether the "exact structure" of a species, nor how many species, of a particular recited element are described in the specification. Instead, the underlying inquiry in determining compliance with the written description requirement is whether the specification describes the claimed invention in sufficient detail that one of skill in the art can reasonably conclude that the inventor had possession of the claimed invention. MPEP § 2163(I) (citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991).

Further, according to the Federal Circuit, Applicants have flexibility in how such "possession" is shown. *See University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886, 1896 (Fed. Cir. 2004). This is particularly the case where a recited element is "auxiliary" to the claimed invention. In *Rochester*, the Federal Circuit cited *In re Herschler*, where the CCPA found that "claims drawn to the use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description ***only so specific as to lead one having ordinary skill in the art to that class of compounds***." *In re Herschler*, 200 USPQ 711, 718 (CCPA 1979) (emphasis provided).

Moreover, it is well-settled that what is well-known or conventional in the art need not be described in detail in the specification. MPEP § 2163(II)(A)(2) (citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986).

In view of the above standards, because the instant invention is not the discovery of ST3Gal-IV sialyltransferase inhibitors, but their use in new methods, and because enzymatic inhibitors of sialyltransferases were known in the art, identification of the inhibitors by their function is entirely proper. Given the state of the art with respect to enzymatic inhibitors of sialyltransferases, the recitation of this function reasonably indicates to the skilled artisan possession of this aspect of the claimed method. Several classes of enzymatic inhibitors of sialyltransferases were well-known in the art as of the effective filing date of the instant application. (*See, e.g.*, specification at page 13, lines 11-25 (citing references.) Such inhibitors include, for example, various structural analogs of sialyltransferase substrates. Analogs of both the donor substrate and acceptor substrate, as well as transition state analogs, had been shown to be useful as sialyltransferase inhibitors. (*See id.*) Thus, the recitation of function in this case would "lead one having ordinary skill in the art" to a class of compounds having this function.

Further, there is no ban on functional language to define an element of an invention. *See In re Feutterer*, 319 F.2d 259, 264, 138 USPQ 217, 221 (CCPA 1963). Indeed, the courts have held that a rejection on this basis under 35 U.S.C. § 112, first paragraph, is improper where the functional language is not used to describe the point of novelty. *See id.* In *Fuetterer*, the invention was a rubber stock composition useful in producing tire treads. The claims included a recitation of "an inorganic salt capable" of maintaining a homogeneous distribution of another component of the composition. The specification listed the function desired and identified four members of the class of inorganic salts having that function. In holding that the description requirement was satisfied, the court focused on the fact that the invention claimed was the combination, not the fact that certain salts have colloid suspending properties. *Id.* at 222, 223. The court went on to state the following:

> The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination. If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have not control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some

> inorganic salt not named by the appellant in his disclosure.
> [*Id.* at 223 (emphasis provided).]

Like the inorganic salts of *Fuetterer*, the sialyltransferase inhibitors recited in the method of claim 1 are defined by their ability to carry out a particular function (inhibiting a certain enzyme), not by their chemical structure. The particular structure of the inhibitor used is not critical to the invention so long as the desired function is achieved. The ruling in *Fuetterer* makes clear that inhibitors not specifically disclosed in the present application are properly within the scope of Applicants' contribution to the art. Thus, the claims should not be so restricted that they can be avoided simply my using an inhibitor different from those specifically exemplified in the application.

Accordingly, in view of the amendments and remarks set forth above, Applicants believe that the present claims satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection is respectfully requested.

***Enablement***

The Examiner bases a rejection of the claims for an alleged lack of enablement on the following contentions:

(1) "unpredictability in the art of antisense nucleic acid therapy";

(2) "lack of guidance as to what particular species of agent or antisense nucleic acids would be required to practice the method as claimed";

(3) "the need to screen multiple species of said agents or nucleic acids so as to allow identification of a particular species as functional within the claimed method and the quantity of *de novo* experimentation necessary to discover the above"; and

(4) "the breadth of the claimed method as an *in vivo* method of prevention or treatment."

(Office Action dated February 10, 2005, at page 18, last paragraph.) Applicants address each of the above assertions in turn.

First, with respect to an alleged unpredictability in the art of antisense nucleic acids, Applicants again note that this aspect of the rejection is obviated in view of the present amendments to the claims to recite an "enzymatic inhibitor of ST3Gal-IV sialyltransferase activity."

Second, as to the Examiner's assertion that the specification lacks guidance as to the species of agent functional in the claimed method, Applicants note that this basis for rejecting the claims for alleged lack of enablement stems largely from the Examiner's position that the claims lack written descriptive support for an "agent" that will function in the claimed method. (*See* Office Action at pages 12 & 13, ¶11.) To the extent that the Examiner relies on an alleged lack of written description for the claimed invention as supporting the enablement rejection, this aspect of the rejection is overcome in part and traversed in part in view of the amendments and reasons set forth above regarding compliance with the written description requirement.

Third, with regard to a "need to screen multiple species of said agents," Applicants disagree with the Examiner's assertion that "the skilled artisan would have to perform an extremely large and undue quantity of de novo trial and error experimentation ... in order to determine, *de novo*, the structure and function of an agent ... that would function to cause an increase or decrease in ST3Gal-IV sialyltransferase activity ...." The Court of Appeals for the Federal Circuit has long recognized that, in determining undue experimentation, "the key word is 'undue,' not 'experimentation.'" *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). This decision makes clear that a considerable amount of experimentation is permissible if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *See id.* *See also* MPEP § 2164.06).

In the present case, an assertion of undue experimentation must begin by acknowledging that sialyltransferases, as a class of enzymes and including ST3Gal-IV sialyltransferase, were well-characterized at the time of the invention. In particular, it was well-known that ST3Gal-IV sialyltransferase catalyzes the transfer of a sialic acid moiety from an appropriate donor substrate (*e.g.*, CMP-sialic acid) to an appropriate acceptor substrate (*e.g.*, Gal$\beta$1,4GlcNAc or Gal$\beta$1, 3GalNAc) to produce a corresponding sialylated product. Moreover,

assays for measuring such ST3Gal-IV activity were also well-known and are described in the specification as filed. (*See* specification at, *e.g.*, page 14, lines 5-27.) As described in the specification, such assays can be used to evaluate the inhibitory activity of a compound. *See id.* There is nothing in the Examiner's rejection to show that such assays were not routine at the time of the invention, nor is there anything in the Examiner's rejection to show that the specification does not provide a reasonable amount of guidance with respect to the direction in which experimentation using such assays should proceed.

Fourth, as to the breadth of the claims as encompassing prophylactic and therapeutic methods, Applicants have shown an *in vivo* effect of ST3Gal-IV sialyltransferase inhibition, *inter alia*, a decrease in levels of vWF and a concomitant decrease in levels of FVIII. Because increased levels of vWF and FVIII are known risk factors for atherosclerosis and are directly involved in blood clotting pathways, the skilled artisan would reasonably accept that *in vivo* inhibition of ST3Gal-IV activity would ameliorate or reduce the risk of such conditions. Therefore, because enzymatic inhibitors of ST3Gal-IV were well-known in the art and could be used by the skilled artisan to inhibit ST3Gal-IV activity, the specification sufficiently enables a therapeutic or prophylactic use of a method for inhibiting ST3Gal-IV as claimed.

In this regard, Applicants also emphasize that the Examiner bears the initial burden of providing evidence or reasoning why a pending claim does not meet the enablement requirement of 35 U.S.C. § 112, first paragraph. The CCPA has stated the following with respect to the Examiner's burden:

> a specification disclosure which contains a teaching of how to use the claimed invention in terms which correspond in scope to those used in the claims *must* be taken as in compliance with the [enablement requirement of § 112, first paragraph,] *unless* there is reason to doubt the objective truth of the statements contained therein .....

*In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971) (emphasis original); *see also* MPEP § 2164.04. It is incumbent upon the Examiner to explain why the truth or accuracy of these statements should be doubted and to provide acceptable evidence or reasoning in support. *See*

*Marzocchi*, 169 USPQ at 370. In the present case, the Examiner has not provided any reasoning or evidence to establish non-enablement of prophylactic or therapeutic use of lowering vWF levels via administration of an enzymatic inhibitor of ST3Gal-IV sialyltransferase.

In summary, Applicants submit that the claims as currently amended are reasonably enabled by the specification. For the reasons set forth above, enzymatic inhibitors of sialyltransferases were well-known in the art, and additional inhibitors could be identified using well-known and routine assays. Further, the specification establishes an *in vivo* biological effect of ST3Gal-IV sialyltransferase inhibition, *inter alia*, a reduction in the levels of vWF and FVIII. Moreover, the association between high vWF/FVIII levels and atherosclerosis or blood clotting disorders were already firmly established in the art. In view of the specification's disclosure and knowledge in the art, the skilled artisan would reasonably expect that enzymatic inhibition of ST3Gal-IV, using known or routinely-identifiable inhibitors, would reduce levels of vWF and FVIII as claimed, and would have a corresponding therapeutic or prophylactic effect against atherosclerosis or blood clotting disorders.

For the reasons set forth above, Applicants believe that the present claims satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection is respectfully requested.

**Rejections under 35 U.S.C. § 102**

Claims 1-5 and 8-12 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Kapitonov *et al.* (U.S. Patent No. 6,280,989). This rejection is overcome in part and traversed in part as follows.

Independent claim 1 as presently amended recites the following:

> A method for modulating levels of vWF or FVIII in an animal, the method comprising
>
> administering to the animal an effective dose of an enzymatic inhibitor of ~~agent that causes an increase or a decrease~~

~~in~~ ST3Gal-IV sialyltransferase activity, wherein said animal is suffering from or is at risk of developing atherosclerosis or a blood clotting disorder, and whereby levels of vWF or FVIII in the animal are decreased.

Support for these amendments is found in the specification at, *e.g.*, page 4, lines 2-4; and page 18, line 11, to page 19, line 16.

Kapitonov does not disclose each and every limitation as presently recited above. In particular, Applicants note that Kapitonov does not disclose administering a ST3Gal-IV sialyltransferase inhibitor to an animal suffering from or at risk of developing atherosclerosis or a blood clotting disorder. Therefore, the present claims are novel over Kapitonov under 35 U.S.C. § 102(e). Withdrawal of the rejection is respectfully requested.

**Rejections under 35 U.S.C. § 103**

Claims 1-5 and 8-12 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Marth *et al.* (U.S. Patent No. 6,376,475) in view of Tsuji.

In view of the present amendments to independent claim 1, Applicants believe the present rejections to be obviated. The Examiner has not shown how the combination of U.S. Patent No. 6,376,475 and Tsuji would motivate one of skill in the art to administer a sialyltransferase inhibitor to an animal suffering from or at risk of developing atherosclerosis or a blood clotting disorder. Therefore, it is submitted that the present claims are patentable over these references. Withdrawal of the rejection is respectfully requested.

**Other Claim Amendments**

New claims 29-39 are added to more fully claim novel aspects of the present invention. Support for these claims in the specification as filed is set forth below.

| Claim(s) | Support |
|---|---|
| 29, 30 | p. 21, ll. 21-24 |
| 31 | p. 15, ll. 21-30 |
| 32 | p. 13, ll. 11-24 |
| 33 | p. 13, ll. 12-22 |
| 34 | p. 13, ll. 12-14 |
| 35 | p. 13, ll. 12-22 |
| 36 | p. 13, ll. 22-24 |
| 37 | p. 18, ll. 28-30 |
| 38 | p. 18, l. 29 |
| 39 | p. 18, l. 30 |

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Dated: 10/10/05 By: _____

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Attachments
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